REMARKS

Applicant respectfully requests reconsideration. Claims 1, 6, 11, 16, 21, 52, 55, 57, 62-68 and 71-76 were previously pending in this application. Claims 1, 11, 21, and 68 have been amended. Claim 76 has been cancelled. No claims have been added. Support for the claim amendments can be found, for example, on page 24, Example 1; on page 8, lines 4-6; on page 11, line 33 - page 12, line 7; and in the claims as filed.

As a result, claims 1, 6, 11, 16, 21, 52, 55, 57, 62-68 and 71-75 are pending for examination with claims 1, 11, 21, and 68 being independent claims.

No new matter has been added.

Rejections Under 35 U.S.C. §103

Claims 1, 6, 21, 52, 55, 57, 62-68, 71, 72, 75 and 76 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Rodriguez-Moran et al. (1999) in view of Rohfling et al. (2000) and Chapin et al. (1999). The Examiner continues to maintain that "[i]t would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made [to] measure serum CRP levels for uses such as characterizing a risk profile for developing diabetes in an apparently healthy individual or evaluating the likelihood that an individual will benefit from treatment given CRP's known association with type II diabetes, as taught by Rodriguez-Moran et al., given that it is well known to measure a known marker for the presence of, or predisposition to, diabetes as taught by Rohfling et al., even in apparently healthy individuals because even apparently healthy individuals can suffer from undiagnosed diabetes and/or complications thereof, as taught by Chapin et al."

The Examiner further asserts that "[k]known disease markers are routinely screened for in 'apparently healthy individuals' …[and] that the claims do not require that subject be disease free."

Without conceding the correctness of the rejection, and solely to expedite prosecution, Applicant has amended claims 1, 11, and 21 to recite that the individual is free of diabetes. Support for this amendment can be found, for example, on page 24, Example 1. Applicant respectfully submits that the subjects in the cited references had diabetes at the time of evaluation. Thus, the combination of cited references do not include all of the elements recited in each of Applicant's

independent claims 1, 11, and 21 as amended. Applicant maintains that none of the cited references either alone or in combination provide any teaching that C-reactive protein (CRP) levels can be used to predict the risk of developing *future* diabetes and diabetes complications in subjects before the diabetic disorder develops.

The Examiner alleges that a "careful review of the Example reveals that the methodology is so flawed as to render the results meaningless. Table 1 clearly shows that the majority of the "Cases" in the study do not meet Applicant's definition of "apparently healthy"" (page 3 of the Office Action).

Applicant respectfully disagrees and would like to bring to the Examiner's attention that care was taken to ensure that the case subjects who participated in the trial described in the specification were free of reported diabetes at enrollment. Due to the high prevalence of undiagnosed diabetes among middle-aged Americans and because the study was designed to evaluate the role of inflammation as a determinant of *future* diabetes, the inventors restricted their case subjects to individuals with baseline hemoglobin A1c <6.5%, which is a reference commonly used in clinical practice (page 25, lines 9-12 of the application as filed). In addition, to reduce misclassification bias due to undiagnosed diabetes at study entry, individuals diagnosed with diabetes within the first year of follow-up were excluded from the study (page 25, lines 1-2 of the application as filed). Moreover, CRP remained a significant predictor after adjusting for body mass index, hypertension, family history of diabetes, exercise frequency, alcohol consumption, hyperlipidemia, smoking and menopausal status (see page 7, lines 12-18 and Tables 2 and 3 – "Adjusted for all risk factors" of the application as filed). Accordingly, elevated levels of CRP in individuals free of diabetes are predictive of an increased risk of diabetes or diabetic complications even after controlling for other factors such as obesity, hypertension, hyperlipidemia, and a family history of diabetes. Thus, the case subjects used in the instant study were free of reported diabetes at the time of enrollment, and every effort was made to reduce misclassification bias due to undiagnosed diabetes and to adjust for a large series of other risk factors.

The goal of the study conducted by Rodriguez-Moran et al. was to identify the relationship between serum CRP and glucose levels in noncontrolled type II diabetic patients (pages 211-212). Rodriguez-Moran et al. does not and could not address the possibility of using CRP levels to predict

the risk of developing future diabetes and diabetic complications in individuals who do not have the disease. Rohfling et al. evaluated the use of GH_b as a screening test for undiagnosed diabetes, and identified subjects who had diabetes which was previously undiagnosed. Rohfling et al. do not teach or suggest that CRP levels or the GH_b screening test can be used to determine the predisposition of a subject to develop *future* diabetes in individuals who are free of diabetes. Similarly, the objective of Chapin et al. was to evaluate the presence of undiagnosed diabetes among US Army soldiers, and not the predisposition to develop *future* diabetes. The subjects identified by Chapin et al. had diabetes which remained undetected until the study was conducted. None of the cited references teach or suggest that CRP levels can be used to predict the risk of developing *future* diabetes in individuals who are free of the disease. Moreover, the skilled artisan would not have combined the cited references in the manner suggested by the Examiner since it was suggested in Rodriguez-Moran et al. that the elevated CRP levels are the result of or are caused by the diabetes. In addition, the choice of a specific level of serum CRP concentration as a significant predictor of the risk of developing future diabetes is taught only in the instant specification.

In conclusion, the combined references do not render obvious the claimed invention at least because the combination of cited references does not yield all the limitations of the claimed invention, and the teachings of the references themselves would not have led the skilled artisan to the combination.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. 103(a).

Claims 1, 6, 21, 52, 55, 57, 62-68, 71, 72, 75 and 76 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Schalkwijk et al. (1999) in view of Rohfling et al. (2000) and Chapin et al. (1999). The Examiner states that "Schalkwijk et al. does not teach the characterizing a risk profile for developing diabetes in an apparently healthy individual" and that "[i]t would have been *prima facie* obvious for one of ordinary skill in the art at the time the invention was made [to] measure serum CRP levels for uses such as characterizing a risk profile for developing diabetes in an apparently healthy individual."

As discussed above, without conceding the correctness of the rejection, and solely to expedite prosecution, Applicant has amended claims 1, 11, and 21 to recite that the individual is free of diabetes. Similar to Rodriguez-Moran et al., Schalkwijk et al. did not evaluate individuals who were free of diabetes. Applicant respectfully submits that the subjects in the cited references had diabetes at the time of evaluation. Accordingly, the combination of cited references do not include all of the elements recited in each of Applicant's independent claims as amended. None of the cited references either alone or in combination provide any teaching that C-reactive protein (CRP) levels can be used to predict the risk of developing *future* diabetes and diabetes complications in subjects before the diabetic disorder develops.

The instant application is based on the discovery that elevated levels of certain markers of systemic inflammation in individuals free of diabetes are predictive of *future* development of diabetes or diabetic complications. In particular, individuals with highest baseline levels of CRP were found to have more than a 10-fold increase in risk of developing *future* diabetes. As stated above, the case subjects used in the instant study were free of reported diabetes at the time of enrollment, and every effort was made to reduce misclassification bias due to undiagnosed diabetes and to adjust for a large series of other risk factors. Schalkwijk et al., on the other hand, measured CRP concentrations in patients with Type I diabetes mellitus. Furthermore, Schalkwijk et al. suggest that these elevated CRP levels may be the result of the diabetic condition rather than the cause of the diabetes (p. 356, right column).

The Examiner contends that the last sentence of Applicant's cite from page 356 of Schalkwijk et al. is "silent regarding the possibility of CRP being present before the onset of diabetes" (page 6 of the Office Action). Applicant respectfully submits that even if the last sentence is silent regarding the possibility of CRP being present before the onset of diabetes, it does not provide the necessary motivation to use CRP levels to predict the risk of developing *future* diabetes in individuals who do not have the disorder. Instead, based on the teachings of Schalkwijk et al., one of skill in the art would conclude that the elevated CRP levels are probably a result of the diabetic condition.

Accordingly, the teachings of Schalkwijk do not render the claimed methods obvious and withdrawal of the rejection is respectfully requested.

Claims 11, 16, 73 and 74 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Rodriguez-Moran et al. (1999) in view of Rohfling et al. (2000) and Chapin et al. (1999) as applied to claims 1, 6, 21, 52, 55, 57, 62-68, 71, 72, 75 and 76, and further in view of Dods and Bolmey et al. (1979). Further, claims 11, 16, 73 and 74 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Schalkwijk et al. (1999) in view of Rohfling et al. (2000) and Chapin et al. (1999) as applied to claims 1, 6, 21, 52, 55, 57, 62-68, 71, 72, 75 and 76, and further in view of Dods and Bolmey et al. (1979).

Applicant respectfully traverses the rejection. The teachings of Rodriguez-Moran et al., Schalkwijk et al., Rohfling et al., and Chapin et al. have been discussed above and are applicable here but are not repeated here. Claims 1, 11, and 21 as amended recite that the individuals are free of diabetes. Dods and Bolmey did not evaluate individuals who were free of diabetes. Instead, 27 patients hospitalized for uncontrolled diabetes mellitus were assayed using the oral glucose tolerance test and the total glycohemoglobin assay. Based on this study, one of ordinary skill in the art could not make any conclusions or predictions regarding the ability of the total glycohemoglobin assay to predict the risk of developing future diabetes in individuals who are free of diabetes.

The instant application is based on the discovery that the predictive value of certain markers of systemic inflammation are independent of other predictors and are at least additive with risk factors such as glycosylated hemoglobin screening. Thus, the level of markers of systemic inflammation does not simply duplicate that which is measured when levels of a second risk factor (e.g., glycosylated hemoglobin) are obtained. Thus, the combination of these two methods of early detection is substantially better than that associated with current methods.

In view of the above arguments, withdrawal of the rejection is respectfully requested.

Rejections Under 35 U.S.C. §102

Claims 1, 6, 21, 52, 55, 57, 62-68, 71, 72, 75, and 76 have been rejected under 35 U.S.C. §102(b) as being anticipated by Ford (1999). The Examiner alleges that since "obtaining a level of C-reactive in a blood sample is the only actual step in the claimed method the reference clearly anticipates the method of the claims" (page 6 of the Office Action).

Without conceding the correctness of the rejection, and solely to expedite prosecution, Applicant has amended claims 1, 11, and 21 to recite that the individual is free of diabetes. The claims as amended are directed to methods for predicting an individual's risk profile of developing future diabetes or a diabetic complication comprising obtaining a level of CRP in a blood sample from an individual and predicting whether the individual has an increased risk of developing future diabetes or a diabetic complication if the level of CRP is about 0.30 mg/dl or higher, wherein the individual is free of diabetes. Ford did not address the possibility of using CRP levels to predict the risk of developing *future* diabetes in individuals who do not have the disease. Ford does not teach that a specific CRP serum concentration (about 0.30 mg/dl) can be used as a significant predictor of future diabetes in individuals who are free of diabetes. Thus, Ford does not anticipate the instant claims because the reference does not teach each and every element of the instant claims.

Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Rejections Under 35 U.S.C. §112

Claims 1, 6, 11, 16, 21, 52, 55, 57, 62-68 and 71-76 have been rejected under 35 U.S.C § 112, second paragraph, as being indefinite. According to the Examiner, "it is unclear whether or not the "characterizing" and "comparing" of the claims are actually steps, or not, and further, precisely what the "characterizing" encompasses. The Examiner alleges that "characterizing" is not defined in the specification, and the metes and bounds of the actual action of the step cannot be determined.

Without conceding the correctness of the rejection and in the interest of expediting prosecution, Applicant has amended claims 1, 11, 21 and 68. The claims as amended are now directed to a method of "predicting" the risk profile of an individual. Support for this amendment can be found throughout the application, for example, on page 8, lines 4-6. According to the MPEP § 2173.02, the test for definiteness under 35 U.S.C. 112, second paragraph, is whether a skilled artisan would understand what is claimed when the claim is read in light of the specification. The term "predicting" is recognized and discernable to one of ordinary skill and allows the reader to apprise the scope of the claim as a whole. A claim term that is not used or defined in the specification is not indefinite if the meaning of the claim term is discernible. *Bancorp Services,*

L.L.C. v. Hartford Life Ins. Co., 359 F.3d 1367, 1372, 69 USPQ2d 1996, 1999-2000 (Fed. Cir. 2004).

Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by the credit card payment, please charge any deficiency or credit any overpayment in the fees to our Deposit Account No. 23/2825, under Docket No. B0801.70238US00.

Dated: June 1, 2010

Respectfully submitted,

By _____

Roque El-Hayek
Registration No.: 55,151
WOLF, GREENFIELD & SACKS, P.C.
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
617.646.8000